INFLAMMATORY BOWEL DISEASES

Summary of Research Goals

Inflammatory bowel diseases (IBD) are a diverse group of digestive tract disorders of often unknown origin and complex disease management. Given the potentially severe impact of these diseases on patients' quality of life, cancer risk, growth and development in childhood and adolescence, and other serious health issues, the Commission proposes a set of research goals that are intended to accelerate progress on understanding, preventing, and effectively managing these diseases in all patients. An urgent research goal is the development of objective criteria for IBD diagnosis and risk evaluation, based on phenotypic and genetic characteristics, which would enable reliable subclassification of patients and their diverse constellations of symptoms. Such validated criteria could facilitate clinical evaluation and disease management approaches that are tailored to individual needs and that improve the efficiency of clinical trials to test new therapies. Strategies to prevent or control IBD that could be tested include modulation of the intestinal microflora or the mucosal immune system. These and other therapeutic approaches are targeted at maintaining the health of the intestinal mucosa and stimulating regeneration and repair in patients with IBD. In addition, finding ways to alleviate the unique developmental challenges faced by children with IBD is a particularly important goal in this research area.

Introduction and Background

Inflammatory bowel diseases comprise a set of chronic inflammatory disorders that affect different sites within the gastrointestinal (GI) tract and are not definitively attributable to any one known etiologic agent or specific precipitant. Two major forms of IBD—designated ulcerative colitis (UC) and Crohn's disease (CD)—have been empirically defined through decades of clinical experience on the basis of characteristic clinical, pathologic, endoscopic, and radiologic features. Occasionally, overlap in some features can prevent a firm diagnosis in a small proportion of patients, who are accordingly said to be affected by indeterminate colitis. Still other patients are affected by a seemingly distinct constellation of chronic idiopathic inflammation designated microscopic colitis (alternatively referred to by its two variants—lymphocytic colitis and collagenous colitis) in which the inflammatory process is milder and manifests primarily as watery diarrhea.

UC is characterized by diffuse inflammation affecting the mucosal and submucosal layers of the colon closest to the luminal surface that typically is most intense in the rectum and can extend proximally to varying degrees. In about a third of patients, the entire large bowel is affected. The inflammation eventuates in mucosal ulceration that contributes to the cardinal symptom of bloody diarrhea. While episodes of inflammatory activity can respond to therapeutic agents, additional "flares" follow with variable frequency. The chronic inflammation increases the risk of colon cancer, making surveillance for dysplasia (a form of pre-cancer) necessary even if the actual inflammatory disease remains in remission.

CD is more varied in its inflammatory process and clinical manifestations. Typically, inflammation affects all layers (referred to as "transmural inflammation"), in contrast to the superficial inflammation found in UC. CD may affect any site within the GI tract from mouth to rectum, though certain site-specific patterns are more common. The terminal ileum is most frequently affected, either alone or in conjunction with some segment of the colon. Similarly, one or more segments of the colon may be affected independent of the terminal ileum or more proximal areas of the digestive tract. In contrast to UC in which the inflammatory process is typically diffuse and continuous in extent, inflammation may be patchy and segmental in CD. Symptoms can reflect the inflammation itself or the scarring that can result (fibrostenotic disease). Often the GI tract becomes obstructed at the affected site. In many patients, the transmural inflammation can result in pathologic connections between the intestine and a variety of

structures, including other parts of the GI tract, the bladder, the vagina, and the skin (most commonly in the perineal or perianal region). Many times, these connections are associated with the formation of abscesses. While CD can result in a wide range of symptoms, patients often experience the combination of abdominal pain, diarrhea, and weight loss. In pediatric patients, lack of growth is a particularly common manifestation. In addition to symptoms related directly to GI tract function, a significant minority of patients with either UC or CD also experience extraintestinal manifestations due to associated inflammation affecting the skin, eyes, joints, liver, and bile ducts. Although specific episodes or complications of CD can respond to available drugs or surgical intervention, none are curative, and disease is lifelong.

It is estimated that more than one million Americans are affected by IBD, with similar numbers for UC and CD. Prevalence is greater among some groups, including those of Ashkenazi Jewish ancestry, but the diseases are found in all ethnic and racial groups. The onset of IBD is most common in the second and third decades of life, though it can begin at any time from infancy to the eighth decade. With onset in early adulthood, these disorders cause many decades of pain and suffering and result in significant lost productivity, in addition to the direct costs of medical and surgical care.

Research suggests that smoking increases the risk of CD, but reduces the likelihood of UC. Appendectomy early in life also appears to reduce the lifetime risk of UC, although the reason remains obscure. Family history appears to be the most significant risk factor. First degree relatives have a five- to 20-fold greater likelihood of developing IBD compared to those from unaffected families. In absolute terms, approximately 5 percent of children of a parent with IBD will develop the disease. The concordance of CD in identical twin pairs may be as high as 50 percent compared to 5-10 percent in non-identical twins, underscoring the key role that genetic inheritance plays in disease susceptibility.

Although a variety of medications are available that can control inflammation and ameliorate the resulting symptoms, none provide fully effective treatment, and almost all are associated with the risk of serious side effects. A variety of formulations that deliver 5-aminosalicylic acid (5-ASA) can be useful in treatment of mild UC and CD and may also diminish the frequency and severity of recurrence in UC. Select patient groups may respond to use of a broad spectrum antibiotic. Patients with more severe inflammation often require corticosteroids, potent anti-inflammatory agents that also carry risk of potentially severe complications, including suppression of normal immune defenses, osteoporosis, hypertension, diabetes, and others. Agents that modulate the immune system, such as azathioprine, 6-mercaptopurine, and methotrexate, are often used to minimize corticosteroid requirements and effect longer term control, but themselves can also cause serious side effects, including bone marrow suppression, pancreatitis, and liver toxicity. More recently, antibodies that target tumor necrosis factor (TNF), a key cytokine, have helped many patients who have not responded adequately to other agents. However, in addition to occasional side effects, the duration of efficacy may be limited, and a significant number of patients fail to respond. Surgical intervention plays a key role in the management of some patients. UC patients with severe disease that fails to respond to medical treatment can be “cured” by total removal of the colon, most commonly with the creation of a neo-rectum (pouch) using the terminal ileum. Surgery in CD patients is usually employed to manage a specific complication of the disease, typically involving drainage of infection and resection of an affected area. However, even when all segments apparently affected are removed, recurrence of CD over time is nearly inevitable. Unfortunately, despite extensive efforts, no effective preventive interventions have been identified for IBD.

Recent Research Advances

IBD genetic susceptibility factors

Substantial progress has been made in identifying factors that collectively appear to underlie the major forms of IBD. Research provides compelling evidence that individual risk for developing IBD depends on the inherited forms of several different genes. These genes control a variety of mucosal functions, particularly those involved in regulating the interaction with and response to luminal microflora. However, genetic inheritance alone is insufficient to lead to IBD, and actual disease depends on environmental factors, likely including the composition of the luminal microflora.

Mucosal barrier function and its functional alteration in IBD

Researchers have gained a more comprehensive—but still incomplete—understanding of the molecular basis of barrier function. Its importance in maintaining normal mucosal homeostasis and its disruption in the pathogenesis of chronic inflammatory bowel disease have been demonstrated. These advances include the composition of the tight junction and its functional regulation. Ultimately, understanding this dynamic regulation should enable strategies for enhancing the barrier to prevent IBD or restore it once damage has occurred.

Key genes conferring risk for IBD

Initial genomic screening led to the identification within the IBD1 region of *NOD2/CARD15*, a gene conferring risk for ileal Crohn's disease in many populations. More large-scale genome-wide scans using haplotypes have led to the identification of several more susceptibility genes, including those encoding the receptor for the cytokine IL-23 and ATG16L1, a protein involved in the process of autophagy and several other processes. Identification of these genes has focused mechanistic studies on the processes that they may mediate, including innate immune response to bacteria and regulation of adaptive immunity. More comprehensive understanding may allow a clinically useful definition of disease risk and prediction of disease course and response to therapy.

Commensal microflora as key drivers of intestinal inflammation

Extensive efforts have failed to consistently implicate a specific pathogen in association with IBD. However, murine models and circumstantial observations in patients provide compelling evidence that the complex variety of commensal microflora, which is innocuous in most people, is an essential driver of chronic intestinal inflammation in susceptible individuals. Thus, development of chronic colitis in murine models requires the presence of a seemingly normal microflora. Characterization of the complexity of normal microflora remains substantially incomplete, though some studies have suggested that at least one class within the microflora—designated AIEC (adherent invasive *E. coli*)—may be more common in CD.

The central role of the epithelium and dynamic interaction between epithelium and luminal bacteria

A variety of direct and circumstantial observations implicate a role for alterations of the epithelial cell compartment in the central pathogenesis of IBD. These include development of colitis in murine models resulting from genetic alterations of epithelial cell-expressed products and expression of proteins encoded by human IBD susceptibility genes in the epithelium. In addition to its role in forming the mucosal surface barrier, the epithelial cell compartment has key capabilities of innate immune response, including expression of both Toll-like receptors (TLRs) and NODs and production of effectors, such as defensins. These may be central to the functional outcome of contact and interaction with luminal microflora—both

commensal populations and enteric pathogens. Alterations in these factors and processes are found in IBD.

IBD involves the loss of mechanisms that normally ensure peaceful coexistence with luminal microflora

Despite possessing a robust variety of receptor and signaling pathways that should trigger inflammation in the context of ubiquitous and constant contact with microflora, the epithelium remains in a state of "tolerance" or hyporesponsiveness. While this hyporesponsive posture allows peaceful co-existence with the omnipresent luminal microflora, it points to important questions for further study, such as: how is this state abrogated in circumstances where inflammation may be a normal and healthy response (e.g., exposure to a true enteric pathogen); and how is it altered in the context of IBD in the absence of a specific pathogen?

Processes mediating innate immune responses and alterations associated with IBD

The finding that the IBD1 genomic region contains a gene encoding an intracellular innate immune receptor protein, as well as the characterization of the full spectrum of receptors, their signaling mechanisms, and effector mediators, underscores the importance of these pathways in mediating normal mucosal homeostasis and alterations that can lead to IBD. The former advance relates to regulation of intracellular bacterial survival and production of the antimicrobial defensin proteins, and the latter relates to altered NOD and TLR receptor forms in patients with IBD. These receptors appear to play a central role in the initial responses to luminal bacteria and, ultimately, result in chronic intestinal inflammation with downstream activation of adaptive immunity.

Processes that effect adaptive mucosal immune responses and their alteration associated with IBD

Researchers have identified several key lymphocyte populations and their cytokine products that drive ongoing intestinal inflammation through stereotypic responses. In addition to the long-recognized Th1 and Th2 responses, these are now known to include Th17 lymphocytes driven by IL-23 and capable of producing IL-17, which leads to release of pro-inflammatory cytokines by target cells and tissue injury, as well as a constellation of FoxP3-positive and -negative regulatory cells. Relative functional deficiency of the latter appears to enable the ongoing inflammation. Dendritic cells and the pivotal role they have in priming these responses have also been defined. Finally, a multitude of cytokine products of these cell populations and others have been identified and their functional effects delineated with the demonstration that many may be particularly important in the pathogenesis of IBD (including, among others: IL-1, IL-2, IL-12, IL-17, IL-23, TNF, interferon, and TGF-β).

Clinical effectiveness of mechanism-based therapeutic agents

Although therapy remains inadequate for many patients and none is curative, anti-TNF treatment has been shown to effect substantial response in some patients who do not respond adequately to other modalities. Other agents targeting mediators and mechanisms identified through recent studies on IBD pathogenesis appear promising in clinical trials.

Mediators of inflammation and tissue injury

As noted above, many cytokines have been found to mediate activation of different cell populations. These cells, in turn, produce a variety of non-peptide effectors of inflammation that include leukotrienes and other prostaglandin-derived products, as well as reactive oxygen metabolites. These appear to be among the most proximate mediators of tissue damage.

Mechanisms of mucosal tissue repair and fibrosis

Many manifestations of IBD can be traced to either failure of normal repair mechanisms to restore mucosal integrity or pathologic repair processes that result in fibrosis and loss of normal physiologic function. Key components of mucosal repair processes, including the contribution of trefoil peptides and some select cytokines, have been identified. Alterations in the balance of production and degradation of extracellular matrix constituents, including the metalloproteinases and the factors that modify them (e.g., TIMPs), have been observed in association with fibrosis in IBD. Definition of key components of the coordinated repair response to injury and the ability to enhance repair through novel strategies for delivering recombinant proteins will play an important role in advancing understanding of IBD, as highlighted by studies of trefoil peptides. These may enable new therapeutics for IBD, complementing those targeted to inflammatory processes *per se*, which may also have particular importance as prophylactic interventions.

Murine models of colitis

Many advances in delineation of processes relevant to IBD have been made possible through the development of murine lines modified by either targeted gene deletion or transgene expression that experience "spontaneous" colitis. These animal models have been used to demonstrate that colitis can result from functional alterations in the epithelial compartment and certain immune processes. The models have also allowed researchers to explore the interaction between genetic susceptibility and environmental factors, including the role of luminal microflora.

Goals for Research[11]

RESEARCH GOAL 5.1: Establish an objective basis for determining clinical diagnosis, detailed phenotype, and disease activity in IBD.

Despite decades of clinical experience, diagnosis of the major forms of IBD remains dependent on empiric criteria that leave important residual uncertainty in a significant minority of patients. Further, despite the well-recognized spectrum of clinical manifestations, objective means are not available to substratify patients in order to predict the natural history of disease or likely responsiveness to different therapeutic agents that would facilitate more effective and efficient therapy. Progress in defining genotypes associated with disease susceptibility, identifying markers of immune response, identifying the central role of luminal microflora, and defining the microbiome of individuals supports the development of rigorous and prospective studies to validate objective criteria that can guide diagnosis and management. Similarly, the rapid evolution of imaging technology reflecting pathophysiologic processes provides an opportunity for functionally meaningful assessment of disease activity. Finally, identification of suitable disease markers that permit objectivity and consistency in diagnosis and subclassification of patients will facilitate and enhance the efficiency of clinical trials.

Objectives:

- Develop a comprehensive genotypic profile.
- Define informative immunophenotypic profiles.
- Develop methodology and applications for a microbiomic profile.
- Develop technology for effective anatomic and functional imaging of disease location and activity.
- Establish useful correlative and predictive biomarkers.

[11] Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.

RESEARCH GOAL 5.2: Develop an individualized approach to IBD risk evaluation and management based on genetic susceptibility.

While significant progress has been made in identifying genetic risk factors for IBD in some broad populations, substantial limitations remain in applying these insights to individuals. Study populations to date have not delineated the relative risks within subpopulations that reflect the full diversity of people who may be affected. Most importantly, substantial gaps remain in understanding the interaction between acquired or environmental factors to determine the mechanisms leading to actual IBD development within individuals. Achieving this overall goal requires a complete understanding of the functional effects of the variant genes that have been found to confer risk of IBD, as well as a comprehensive matching of disease-associated genotypes to disease features and response to therapy. Genes that metabolize agents used in the management of IBD need to be investigated with respect to their influence in modulating response to therapy and potential toxicities. Undertaking a multi-dimensional and comprehensive study of IBD-associated genes and their products is a critical component of this goal.

Objectives:
- Complete identification of risk susceptibility genes among diverse patient populations.
- Determine the functional role of IBD-associated gene variants in pathophysiologic pathways leading to IBD.
- Determine the impact of environmental factors on disease-associated genetic variants.
- Define genetic subset/phenotype-genotype correlations.
- Identify and assess relevant pharmacogenetic variations.
- Correlate genotype (disease susceptibility and pharmacogenetics) with response to therapy and incorporate genotypes into clinical trials.
- Use genotypic variations to define disease risk.

RESEARCH GOAL 5.3: Modulate the intestinal microflora to prevent or control IBD. (See also Goals 1.20, 1.21, and 9.3.)

The convergence of insights derived from experimental and clinical observations points to a central role of the luminal microflora as a driver of chronic IBD. While research proceeds in defining host factors that contribute to the development of an immune and inflammatory response that overrides the tolerance to luminal microflora found in healthy individuals, understanding of the complex populations of microbes that constitute the luminal microflora is markedly incomplete. Beyond the intrinsic complexity of the microflora, a major barrier to defining the combination of microbes and/or their products that are important in the pathogenesis of IBD in populations and individuals is the inability of current technologies to resolve this complexity. Development of large-scale sequencing and corresponding powerful computational tools is essential to understanding the role of the microflora in IBD pathogenesis. Insights derived from the application of these tools can also provide a foundation for the development of strategies for effective therapeutic manipulation of luminal microflora content, which conceptually should be free of risk for adverse side effects.

Objectives:
- Achieve a comprehensive molecular and functional delineation of the intestinal microflora in all relevant niches across different individuals/populations.
- Understand the factors that regulate the composition and functional characteristics of the intestinal microflora, including host factors (e.g., environmental, genetic, and mucosal function).
- Characterize the intestinal microflora associated with IBD by location and disease activity.
- Develop experimental tools for understanding intestinal microbiome complexity and clinical methods for characterization and monitoring of the intestinal microflora in patients.

- Develop experimental *in vivo* systems for preclinical studies of intestinal microflora therapeutic modulation.

RESEARCH GOAL 5.4: Effectively modulate the mucosal immune system to prevent or ameliorate IBD.

It is axiomatic that immune activation and the production of inflammatory mediators are intrinsic to IBD, in which the presence of infiltration with cells associated with these responses is among the defining empiric criteria of these disorders. Substantial progress has been made in defining the components of mucosal innate and adaptive immune responses. However, a comprehensive understanding of these complex pathways is still needed as a foundation for understanding their activation and alteration in the context of IBD. This will require developing molecular signatures of all immune cell populations, the factors regulating their activation, and their products. The intricate interconnection among the cell populations participating in immune and inflammatory responses and the multiplicity of their products demand a systematic approach and the quantitative strategies of systems biology. Given the mounting evidence for the pivotal role of luminal microflora in IBD, it is essential to delineate the interactions among these flora, the immune response, and the factors that deregulate the processes that allow tolerance in the normal intestine. Determining the total components of the immune and inflammatory response should enable the development of strategies for focused modulation to achieve effective control of these responses without the toxicities that result from the relatively non-specific and broad immunosuppressive effects of most current therapies.

Objectives:
- Define all relevant immune cell populations by their functional characteristics and differentiation pathways.
- Define the factors regulating innate and adaptive immunity, both genetic and environmental.
- Delineate innate and adaptive immune interaction with the microbiome.
- Identify relevant inflammatory mediators in effecting IBD injury and symptomatic manifestations of IBD and mechanisms regulating inflammatory processes.
- Characterize alterations in innate and adaptive immune function in IBD, including regulatory cell populations, especially related to microbiome.

RESEARCH GOAL 5.5: Sustain the health of the mucosal surface.

Normal intestinal function depends on the integrity of the mucosal surface. Research indicates that the epithelium may be intrinsically altered by genetic and other factors that play a role in the initiation of IBD. Conversely, the epithelium is the victim of the inflammatory processes that lead to mucosal ulceration, a central process underlying IBD that permits sustained activation of underlying immune and inflammatory responses. Understanding the biology of the epithelium will provide insights into the earliest and most central events that lead to the major forms of IBD and create a foundation for developing strategies to enhance the functional and physical integrity of the mucosal surface. Defining the role of the epithelium in these disorders depends on integrated study of the interaction of this surface compartment with the luminal microflora at its apical surface and the variety of cell populations within the underlying lamina propria. It is equally important to define the distinct roles of the four major cell lineages (columnar, goblet, Paneth, and enteroendocrine) that collectively comprise the epithelium, given that functional alterations in each cell type are associated with IBD. Investigating the intestinal stem cell compartment and the processes regulating the production and differentiation of cells emerging from progenitor populations is an important aspect of this goal.

Objectives:
- Understand the functional biology of the epithelial compartment and identify alterations in IBD.
- Identify and characterize the stem cell compartment and develop the capacity to modulate lineage specification and maturation.
- Understand the structural and functional elements of the mucosal barrier, including the role of luminal microflora and nutrients, and alterations associated with IBD.
- Define the systems biology of the intestinal mucosa, including interactions among epithelial and lamina propria cell populations, as well as integration with enteric nervous, endocrine, and vascular elements.

RESEARCH GOAL 5.6: Promote regeneration and repair of injury in IBD.

In parallel with the goal of sustaining the health of the mucosal surface, effective treatment of patients with established IBD will utilize insights in mucosal biology to promote repair of injury resulting from inflammatory processes. Such therapies should aim to restore structural integrity and physiologic function to affected sites within the GI tract. For many patients, the morbidity of their disease results more from the failure of healing with ongoing ulceration or a pathologic healing response and resultant fibrosis and/or loss of mucosal function than from the effects of inflammation *per se*. Effective interventions to promote physiologic repair will depend on knowledge of the processes that contribute to tissue healing. Understanding the factors contributing to fibrosis and the mechanisms that allow remodeling of the extracellular matrix will be particularly important given the frequency at which fibrosis leads to obstruction and other morbidity. Strategies to improve functional capacity are also important for the many patients in whom the disease process leads to extensive mucosal destruction, as well as the many others who currently require extensive surgical resection.

Objectives:
- Understand normal repair processes and characterize their alteration in IBD.
- Define the impact of the intestinal microflora on tissue repair.
- Develop strategies to modulate repair processes to restore functional capacity.
- Identify mechanisms to reverse or remodel fibrotic response.
- Identify interventions that improve care of patients with surgically modified gut.

RESEARCH GOAL 5.7: Provide effective tools for clinical evaluation and intervention in IBD.

While prevention of IBD is the ultimate goal, more effective tools for the evaluation of disease activity are needed to guide therapy, and more effective therapeutic agents are needed for the many patients for whom currently available modalities are ineffective or counterbalanced by adverse effects. New tools should include noninvasive modalities for rapid assessment of the distribution and intensity of inflammatory activity. Identification of early markers of inflammation, as well as markers that predict ultimate response soon after initiation of a new therapeutic intervention, will be powerful adjuncts to both routine clinical management and a means of accelerating the speed and efficiency of clinical trials of new agents. Finally, it is essential that evolving insights into the critical pathophysiologic mechanisms that lead to IBD are used to develop more specific therapeutic agents and other interventions that fill the unmet treatment needs of IBD patients.

Objectives:
- Develop and validate technologies to evaluate disease status, including biomarkers, as well as noninvasive and other novel endoscopic imaging methods.
- Develop innovative endoscopic and more physiologic surgical interventions.

- Develop effective and non-toxic mechanism-based pharmacologic therapies, including manipulation of the microflora.
- Develop tools for more efficient clinical development of investigational agents, including surrogate markers of response.
- Develop tools to more effectively identify pre-malignant changes in the mucosa and support interventions to reduce cancer risk.

RESEARCH GOAL 5.8: Ameliorate or prevent adverse effects of IBD on growth and development in children and adolescents.

In addition to the challenges faced by adult patients with IBD, children and adolescents face distinctive clinical manifestations unique to these patient groups due to the potential impact of the disease on normal growth and development. Indeed, the lack of growth can be the most prominent manifestation in childhood, and the failure to undergo a normal growth spurt in young adolescents with IBD has potential lifelong impact. This impact extends from limitations in physical stature to difficulties in social and emotional maturation that can follow. These potentially profound effects on growth reflect a variable combination of the influence of inflammatory mediators, malabsorption resulting from mucosal injury, and poor nutritional intake. In addition to the effects of IBD, drugs used to treat the disease may have a negative impact on overall growth. Accordingly, strategies are needed to ensure normal growth and development in these vulnerable patient groups, in concert with overall efforts to treat the IBD.

Objectives:
- Develop interventions that promote normal social interactions and mental health in all children and adolescents with IBD.
- Define the mechanisms that produce growth delay in pediatric IBD patients.
- Identify approaches that enable normal growth and development within the context of pediatric IBD.

Major Challenges and Steps To Achieve the Goals

Basic Mechanisms of IBD

To build on recent progress in defining IBD susceptibility genes, large-scale collaborations (national and international) would facilitate comprehensive sample acquisition, analysis of genetic loci across diverse populations, and research on well-characterized patients followed on a longitudinal basis to define genotype-phenotype correlation. Even more challenging are the current methodological limitations for the study of complex microbial populations in the GI tract. The development and dissemination of rapid, quantitative, high-throughput techniques to define individual members of complex microbial communities, robust bioinformatic tools, and metagenomic data sets with comprehensive data on provenance and host phenotype would accelerate progress in the field. New computational tools, such as *in silico* techniques for modeling microbial populations and microbial-host interactions, would enable researchers to effectively mine extremely large data sets. Initiating an intestinal microbiome project, beginning with commissioning computational tools and pilot projects, represents an important step to addressing these challenges. The establishment of the Human Microbiome Project within the NIH Roadmap for Medical Research provides essential technologies and resources for research on the intestinal microbiome. An equally important and technically difficult hurdle is the development of techniques to isolate and sustain primary epithelial cell populations *in vitro* to enable research on these critical cell populations and their functional alteration in IBD.

Translational Research

With acceleration of the discovery of susceptibility genes and basic mechanisms of immune response and epithelial function, the opportunities for translational research in the context of IBD are greater than ever. In order to realize the potential for new insights into disease processes, it is important to develop robust *in vitro* model systems, including primary cell and organ cultures, that recapitulate the complexity of intestinal mucosa and can be experimentally manipulated. Parallel development of animal models with validated clinical relevance in which response to intervention is predictive of response in humans would enable rapid progress from *in vitro* systems to animal model studies to patients. Better integration of basic and clinical research efforts is essential for more effective translational progress. Establishing consortia of investigators across institutions would expedite research to understand the functional implications of the gene variants that have been associated with IBD.

Clinical Research and Discovery

The lack of objective and consistent criteria for diagnosis and substratification of patients remains a significant barrier. Fully realizing the opportunities to develop and evaluate new therapies based on growing insight into IBD pathophysiology depends on establishing standards for clinical trials, including incorporation of surrogate endpoints, phenotyping, and DNA collection. Standardization of techniques for DNA sample acquisition would also foster close integration with translational studies. Overall, the potential synergies between clinical studies and translational analysis have not been realized and, thus, provide an opportunity to accelerate the assessment of basic mechanisms elucidated through study of animal models and *in vitro* systems within the context of human IBD. Equally important, development of more effective strategies for enrolling patients in clinical trials and fostering the development of a larger cadre of clinical investigators and clinical trial infrastructure would support an expanded national and international program of interventional clinical trials for IBD. Particular attention should be paid to overcoming barriers to therapeutic trials in pediatric populations, such as industry reluctance due to potential risks in these patient groups. These efforts, as well as more basic and translational research challenges, would benefit substantially from greater public awareness and understanding of IBD that can be achieved through public educational programs. Convening a clinical summit on IBD attended by investigators, all stakeholding agencies, and industry would be an initial step toward surmounting these challenges.